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Prospective Randomized Trial of Empiric Therapy with Trimethoprim-Sulfamethoxazole or Doxycycline for Outpatient Skin and Soft Tissue Infections in an Area of High Prevalence of Methicillin-Resistant *Staphylococcus aureus*▽

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To evaluate empirical therapy with trimethoprim-sulfamethoxazole or doxycycline for outpatient skin and soft tissue infections in an area of high prevalence of methicillin-resistant *Staphylococcus aureus*, a randomized, prospective, open-label investigation was performed. The overall clinical failure rate was 9%, with all failures occurring in the trimethoprim-sulfamethoxazole group. However, there was no significant difference between the clinical failure rate of empirical trimethoprim-sulfamethoxazole therapy and that of doxycycline therapy.

Skin and soft tissue infections (SSTI) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) acquired in the community have rapidly increased in prevalence over the past decade (6, 7, 9, 11). With this shift in the epidemiology of SSTI, empirical therapy for SSTI with β-lactams is often no longer thought to be acceptable in those clinical situations where antibiotic therapy is deemed to be necessary. While retrospective and observational data for the use of off-patent oral antimicrobials, such as tetracyclines, trimethoprim-sulfamethoxazole, and clindamycin, for treating MRSA SSTI have shown these agents to be effective, prospective randomized data for this therapy are largely unavailable (1, 2, 3, 8, 11).

As MRSA is more likely to be isolated from an SSTI than a β-lactam-susceptible organism at Parkland Hospital in Dallas, Texas, we performed a randomized, prospective, open-label investigation in our emergency department to determine the efficacy of empirical therapy using off-patent oral antibiotics (trimethoprim-sulfamethoxazole, 160 mg/800 mg twice daily, or doxycycline, 100 mg twice daily for 7 days) for the outpatient treatment of SSTI abscesses requiring wound packing after incision and drainage but not requiring hospitalization. Only patients with SSTI requiring wound packing were enrolled, to eliminate the inclusion of patients with smaller SSTI that did not require wound packing.

This investigation was approved by the University of Texas Southwestern Medical Center institutional review board and included adults (≥18 years old) who were willing and able to provide informed consent. Inclusion criteria included the abilities to return for follow-up examination at 2 to 5 days after enrollment and to be accessible by telephone for follow-up assessment at 10 to 14 days and 28 to 35 days after enrollment. Exclusion criteria excluded patients with contraindications or a history of hypersensitivity reaction to any of the study treatment regimens, an infected prosthesis or device, concomitant bacteremia or deep-seated infections, diabetic foot infections, and known immunodeficiency conditions and those who were pregnant or breastfeeding, required additional antimicrobial agents, and did not obtain assigned antibiotics.

The primary endpoint of this study was clinical failure, defined as a subsequent hospital admission, the administration of intravenous antibiotics, or a change in oral antibiotics over a period of 10 to 14 days after the initial emergency department presentation. Repeated outpatient incision and drainage of the SSTI at 2 to 5 days after enrollment were not considered a clinical failure, if the antibiotic regimens were not changed and intravenous antibiotics were not administered. The trial enrolled patients from October 2005 to May 2006. Fisher's exact test was used for statistical analysis.

Forty subjects were enrolled; however, six of these subjects, all of whom had been randomized to the trimethoprim-sulfamethoxazole group (three did not obtain the assigned antibiotic, and three did not have a working phone number), were excluded. Baseline characteristics for the 34 subjects meeting the study criteria are presented in Table 1 and Table 2 (there were no differences in baseline characteristics between the treatment groups). Outcomes at 10 to 14 days after initial emergency department presentation were available for 33 of 34 subjects (one subject was lost to follow-up in the doxycycline group). Outcomes at 28 to 35 days after initial emergency department presentation were available for 31 of 34 subjects (three subjects were lost to follow-up in the doxycycline group).

Twenty-three of 34 (68%) abscess cultures were positive for MRSA. All MRSA isolates were susceptible, in vitro, to trimethoprim-sulfamethoxazole (MIC, ≤2/38 μg/ml) and tetracycline (MIC, ≤4 μg/ml). Four of 34 (12%) abscess

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TABLE 1. Patient characteristics

Patient characteristic	Patient data (n = 34)	% of data
Mean age (range)	38 yr (18–72)	
Race		
African American	20	58.8
Caucasian	6	17.6
Hispanic	8	23.5
Fever by history	7	20.6
Fever on exam	0	0
Pain	34	100

TABLE 2. Abscess characteristics

Abscess characteristic	Patient data (n = 34)	% of data
Abscess location		
Torso and neck	6	17.6
Axilla	7	20.6
Upper extremity	8	23.5
Inguinal and gluteal	3	8.8
Lower extremity	10	29.4
Fluctuance	34	100
Tenderness	34	100
Erythema diameter[a]		
Mean ± SD (cm)	7.2 ± 4.9	
Median (cm)	6.5	

[a] Data represent median and mean measurements ± standard deviation (SD) of the means in cm.

cultures were positive for methicillin-sensitive *Staphylococcus aureus*, and 2 of 34 (6%) were culture negative (other abscess isolates included coagulase-negative staphylococci, *Corynebacterium* species, *Streptococcus milleri*, and "gastrointestinal flora").

Of the 34 subjects included in the study, 14 received trimethoprim-sulfamethoxazole (8 with MRSA) and 20 received doxycycline (15 with MRSA). One subject with MRSA was lost to follow-up in the doxycycline group. Three of the 33 subjects (9%) with data at 10 to 14 days were classified as clinical failures. All 3 clinical failures occurred in the trimethoprim-sulfamethoxazole group (3 failures out of 14 [21%] subjects on trimethoprim-sulfamethoxazole therapy), with no clinical failures in the doxycycline group. By culture, two of the clinical failures with trimethoprim-sulfamethoxazole had MRSA, and one had *Streptococcus milleri*. All three clinical failures were hospitalized due to worsening of the initial SSTI, which subsequently improved with no other complications. By intention-to-treat analysis (the one subject lost to follow-up in the doxycycline group was considered a failure), a comparison of the treatment groups showed there were no statistically significant differences in failure rates ($P = 0.283$). Three patients in each treatment group required repeated outpatient incision and drainage at 2 to 5 days after enrollment. All other subjects reported good response at 10 to 14 days after initial presentation.

Telephone follow-up at 28 to 35 days after initial presentation with 31 of 34 subjects found that 3 of 14 (21.4%) subjects in the trimethoprim-sulfamethoxazole group and 3 of 17 (17.6%) subjects in the doxycycline group had recurrent SSTI; all recurrent SSTI were at new sites. No other complications were noted. None of the patients lost to follow-up was admitted to Parkland Hospital over the course of the study or at 1 month after study completion, by review of electronic records.

While virtually all of the existing data for the efficacy of off-patent oral antimicrobials used in treating MRSA SSTI are observational or retrospective in nature, this trial begins to provide needed prospective randomized data for empirical therapy with trimethoprim-sulfamethoxazole or doxycycline for outpatient SSTI in an area of high prevalence of MRSA. We chose trimethoprim-sulfamethoxazole and doxycycline as they are less expensive oral antimicrobials with similar twice-daily dosing. In addition, community-associated MRSA has low rates of resistance to both trimethoprim-sulfamethoxazole and doxycycline, while community-associated MRSA resistance rates for clindamycin and fluoroquinolone may be too high for these agents to be considered for empirical treatment of SSTI in some regions of the United States (2, 4, 6, 11).

The occurrence of all failures in the trimethoprim-sulfamethoxazole group of empirical treatment of SSTI needs to be evaluated in a large and blinded trial. A higher dosage of trimethoprim-sulfamethoxazole may be more efficacious than the dosage used in our investigation, as has been suggested by some groups (10). However, trimethoprim-sulfamethoxazole may not provide an antimicrobial spectrum of activity that is adequate to empirically cover *Streptococcus* species in SSTI, as was seen in the failed cases in which *Streptococcus milleri* was isolated (2).

Importantly, as it has been shown that many community-associated MRSA SSTI can be adequately managed with incision and drainage alone, without the use of antimicrobials, further investigation is also needed to better determine which SSTI require antimicrobials and which do not (5, 6, 11). Possibly, the failure rate of 21% found with trimethoprim-sulfamethoxazole in our study may be the same as the failure rate expected with incision and drainage of SSTI without the use of antimicrobials.

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